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# Perception and acceptance of the use of 0.2% polyhexanide *versus* 0.12% chlorhexidine digluconate in patients at a risk of developing oral mucositis.

## Percepción y aceptación del uso de polihexanida al 0.2% *versus* digluconato de clorhexidina al 0.12% en pacientes con riesgo de desarrollar mucositis oral.

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**Abstract: Objective:** To evaluate the perception and acceptance of using polyhexanide (PHMB) and chlorhexidine digluconate (CLX) in individuals at a risk of developing oral mucositis induced by chemoradiotherapy. **Materials and Methods:** This is a randomised comparative study. Participants were randomised into two groups: Group 1 (PHMB 0.2%) and Group 2 (CLX 0.12%), these groups performed a mouth rinse with the respective solutions for 1 minute every 12 hours during an antineoplastic treatment cycle. The participants were evaluated at three different times: before ($t_0$), during ($t_1$) and after a cycle of antineoplastic treatment ($t_2$). Severity of oral mucositis (OM), mouth pain, quality of life (OHIP-14), oral hygiene index and assessment of the acceptance of the substances in the mouth were assessed. **Results:** There were 23 individuals, 12 in Group 1 (G1) and 11 in Group 2 (G2). Both groups presented with OM in all three evaluations. Reported mouth pain was lower in G1 than in G2. The PHMB had a better acceptance ($p$=0.012) than the CLX for the time of mouth rinse at t0. There was a lower impact in the quality of life from oral health in the physical pain aspect ($p$=0.019) and in social incapacity ($p$=0.037) in G1 than in G2. **Conclusions:** PHMB has the same acceptance compared to CLX and is a good option for antiseptic mouth rinse with less adverse effects.

*Keywords: Mouthwashes; chlorhexidine; polyhexanide; quality of life; oral health; oral mucositis.*

**Resumen: Objetivo:** Evaluar la percepción y aceptación del uso de polihexanida (PHMB) y digluconato de clorhexidina (CLX) en individuos con riesgo de desarrollar mucositis oral inducida por quimiorradioterapia. **Materiales y Métodos:** Eeste es un estudio comparativo aleatorizado. Los participantes fueron asignados al azar en dos grupos: Grupo 1 (PHMB 0.2%) y Grupo 2 (CLX 0,12%), estos grupos realizaron un enjuague bucal con las soluciones respectivas durante 1 minuto cada 12 horas durante un ciclo de tratamiento antineoplásico. Los participantes fueron evaluados en tres momentos diferentes: antes ($t_0$), durante ($t_1$) y después de un ciclo de tratamiento antineoplásico ($t_2$). Se evaluaron la gravedad de la mucositis oral (OM), el dolor de boca, la calidad de vida (OHIP-14), el índice de higiene oral y la evaluación de la aceptación de las sustancias en la boca. **Resultado:** Hubo 23 individuos, 12 en el Grupo 1 (G1) y 11 en el

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Grupo 2 (G2). Ambos grupos presentaron OM en las tres evaluaciones. El dolor de boca informado fue menor en G1 que en G2. El PHMB tuvo una mejor aceptación ($p$=0.012) que el CLX para el momento del enjuague bucal en t0. Hubo un impacto menor en la calidad de vida de la salud bucal en el aspecto del dolor físico ($p$=0.019) y en la incapacidad social ($p$=0.037) en G1 que en G2. **Conclusion:** PHMB tiene la misma aceptación en comparación con CLX y es una buena opción para el enjuague bucal antiséptico con menos efectos adversos.

***Palabra Clave:*** *Antisépticos bucales; clorhexidina; polihexanida; calidad de vida; salud bucal; mucositis.*

## INTRODUCTION.

Polyhexanide (PHMB) is an antiseptic, characterized by a wide spectrum polymeric biguanide, that active against both Gram-positive and Gram-negative bacteria by acting on the cell membrane causing cell lysis of the microorganisms.[1,2]

Individuals undergoing anti-neoplastic treatment are advised to use oral antiseptics to control bacterial plaque and also to avoid secondary infections, especially during the period of oral mucositis (OM) induced by chemoradiotherapy.[3,4] In order to improve oral health, chlorhexidine digluconate (CLX), a cationic biguanide, has been widely recommended because of its wide spectrum antibacterial effect.

Although it is considered a gold standard for plaque control, it has some undesirable adverse effects when used over a long period, such as taste alterations, pain, xerostomia and a risk of staining teeth and restorations.[5,6]

Faced with all the adverse effects of CLX, it was necessary to search for alternative treatments. A study looking into the application of antiseptic agents in cutaneous wounds showed a higher biocompatibility of PHMB compared to CLX, iodopovidone, triclosan, silver, and sulfadiazine.[6] PHMB was used for several years as an antiseptic solution in medical applications without evidence of bacterial resistance when used topically on skin, eyes, and wounds.[7-8] It has also shown little toxicity, has a good safety record, good efficacy, low cost, and tolerability.[10,11]

In dentistry, the inhibitory action of PHMB as an antiseptic in the formation of oral biofilm has been studied, showing a reduction in the amount of bacteria.[12,13] This suggests that these solutions may be an alternative treatment for the prevention of secondary infections such as in oral mucositis ulcers.

When OM is present in the mouth, it can act as a reservoir of pathogenic microorganisms, because this pathology increases the severity and impacts the quality of life and survival of individuals undergoing antineoplastic treatment.[14-16]

Thus, the introduction of PHMB as a mouth rinse provides a good opportunity to incorporate a safe, effective, less toxic antiseptic agent that may be more acceptable for prolonged use as PHMB offers additional alternatives and tools for oral microbial control.

Therefore, the aim of this study is to evaluate the risk of developing oral mucositis induced by chemoradiotherapy in patients, comparing the acceptance of PHMB and CLX as buccal mouth rinses and their perception about the quality of life.

## MATERIALS AND METHODS.

This study was approved by the Research Ethics Committee of the institution where it was carried out (CAEE 48742115.1.0000.5417).

A prospective randomized double-blind trial was conducted in individuals with cancer who were undergoing dental treatment in a clinical research center and agreed to participate in the survey through the signing of written informed consent. Individuals were assessed for risk of developing oral mucositis at pre-cycle, during, and post-cycle of antineoplastic treatment. Individuals under 18 years of age, individuals with allergies to the products used and those who did not want to participate in the study were excluded from the protocol.

The total number of participants was divided into two groups (G1 and G2) and these were distributed through randomization using the Microsoft Excel software. G1 patients used the 0.2% polyhexanide solution (Prosept®) as a mouth rinse, and the G2 patients used the 0.12% non-alcoholic chlorhexidine digluconate solution. The groups were instructed to carry out a mouth rinse with 5 ml of solution for one minute every 12 hours for the duration of one cycle of antineoplastic treatment.

The solutions were distributed to the patients by the researcher, and the evaluators of the participants were blinded. The flasks of the solutions were randomized through the Microsoft Excel software and divided

into flasks of the same color (milky white). These were randomly distributed by the research advisor, who was the only one to know which the distributed substances were.

### Study Design

The individuals were evaluated in three stages: immediately before starting radiotherapy and/or chemotherapy sessions ($t_0$), during antineoplastic treatment ($t_1$), after 15 to 20 radiotherapy sessions and if chemotherapy between the 5th and 7th day, and the third ($t_2$) time after the end of the antineoplastic treatment cycle.

### Oral Mucositis Evaluation

Oral mucositis was evaluated and classified according to World Health Organization (WHO). This ranges from 0 to 4:

(0) The absence of OM,

(1) The presence of pain and erythema,

(2) The presence of ulcers and/or erythema with a solid diet,

(3) The presence of ulcers with liquid or paste feeding and

(4) The presence of ulcers that prevents feeding.[17]

### Pain Evaluation

The Visual Analogue Scale (VAS)18 was performed to assess the level of discomfort during the days that followed the use of the substances (on three occasions). For this, a 10 cm ruler divided into 10 parts was presented, with the number zero in an extremity and the other end with the number ten. The patient was asked about the level of pain, considering 0 as no pain and 10 as the worst possible pain.

### Assessment of Impact on Quality of Life by Oral Health

The evaluation of the Impact on Quality of Life by Oral Health was performed through the application of the OHIP-14 (Oral Health Impact Profile) questionnaire. The OHIP-14 is composed of 14 questions, subdivided into seven parts: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap. The impact value of each part was classified as weak, medium or strong. The overall impact was obtained by calculating the sum of the impacts of the seven different parts.[19]

### Assessment of Oral Hygiene

For the assessment of oral hygiene, the Oral Hygiene Index (OHI) was used, this measures the amount of plaque and calculus on the buccal and lingual surfaces of the first molars and incisors. A score ranging from 0 to 3 was given, for both plaque and calculus, and the higher the value, the worse the patient's oral hygiene condition.[20]

### Assessment of the acceptance of the substances in the mouth

Aiming to assess the action of the substances in the oral cavity, this study created a questionnaire composed of seven questions carried out three times:

1: Was rinsing with the solution, delivered by the researcher, both possible and tolerable?

2: How long did the person cope with keeping the solution in the mouth while washing?

3: Was such rinsing impossible at some point?

4: Did the solution present a sweet or bitter taste?

5: Was there a burning sensation while rinsing with the solution?

6: Was there any dry mouth after rinsing with the solution?

7: Was there some discomfort after rinsing with the solution?

### Statistical analysis

Data collected were tabulated and statistically analyzed using the Statistics© version 12.0 software. For the quantitative variables, the Kolmogorov-Smirnov statistical test was used. To make a comparison between both groups, the Mann-Whitney test was used for the quantitative variables, and Fisher's exact test was used for the qualitative variables.

## RESULTS.

Forty randomized individuals were recruited for the research according to the methodology described. Of these, eight refused to participate, resulting in 32 individuals available. During the evaluations, in G1, one patient died and three did not continue the research, while in G2, there was one death and four did not continue, leaving 12 individuals in G1 and 11 in G2. Epidemiological data (age, gender, type of tumours, type of treatment and chemotherapy) Table 1.

Regarding the presence of oral mucositis (Table 2), at $t_0$, only one patient in each group had OM grade II, as a consequence of a previous cycle of chemotherapy. At $t_1$, in G1 only one (8.3%) of the patients had OM and this was grade I, whereas in G2, 4 (33.2%) patients had OM, two of which grade II. There was no significant difference between the groups in the evaluations.

In group 1, VAS had the lowest mean value (0.17) at $t_2$ and the highest (0.92) at $t_1$. While in group 2, the VAS had the lowest mean value (0.27) at t0 and the highest (2.09) at $t_1$.

Both groups had the lowest VAS before the onset of anti-neoplastic treatment, the longest during treatment and a lower value after G1 but not G2 (Table 3).

Regarding the acceptance of the substances in the oral cavity, in the question *"time the patient was able to keep the solution in the mouth for mouth rinsing"*, 100% of G1 patients maintained mouthwash for one minute at all three times. While in G2, 18% of the patients maintained the mouth rinse for less than one minute at $t_0$ ($p$=0.012).

Regarding the flavor of the solutions (bitter or sweet),

**Table 1.** Demographic data from analyzed Groups G1 and G2.

| | Age | Mean | SD | Mean | SD |
|---|---|---|---|---|---|
| | | 59.42 | 12.003 | 56.27 | 9.14 |
| | | N (%) | | N (%) | |
| Gender | Female | 7 (58.33) | | 5 (45.45) | |
| | Male | 5 (41.67) | | 6 (54.54) | |
| Type of Tumor | Colon | 4 (33.4) | | 2 (18.2) | |
| | Breast | 3 (25) | | 2 (18.2) | |
| | Lung | 1 (8.3) | | 1 (9.1) | |
| | Oropharynx | 1 (8.3) | | 1 (9.1) | |
| | Tongue | 1 (8.3) | | 1 (9.1) | |
| | Nasopharynx | 0 (0) | | 2 (18.2) | |
| | Bladder | 0 (0) | | 1 (9.1) | |
| | Esophagus | 0 (0) | | 1 (9.1) | |
| | Prostate | 1 (8.3) | | 0 (0) | |
| | Non-Hodgkin's lymphoma | 1 (8.3) | | 0 (0) | |
| Type of Treatment | QT (Chemotherapy) | 10 (83.3) | | 8 (72.7) | |
| | RT (Radiotherapy) | 2 (16.7) | | 2 (18.2) | |
| | QT + RT (Chemotherapy + Radiotherapy) | 0 (0) | | 1 (9.1) | |
| Type of Chemotherapy | 5-Fluorouracil + Oxoplatina | 0 (0) | | 1 (9.1) | |
| | Cisplatin + Gemcitabine | 0 (0) | | 1 (9.1) | |
| | Cisplatin | 0 (0) | | 2 (18.2) | |
| | Doxorubicin + Cyclophosphamide + Paclitaxel | 1 (8.3) | | 1 (9.1) | |
| | Epirubicin + Doxorubicin | 0 (0) | | 1 (9.1) | |
| | Capecitabine | 0 (0) | | 1 (9.1) | |
| | Doxorubicin + Paclitaxel | 1 (8.3) | | 0 (0) | |
| | FOLFOX | 1 (8.3) | | 0 (0) | |
| | Irinotecan + Bevacizumab | 1 (8.3) | | 0 (0) | |
| | Carboplatin + Paclitaxel | 1 (8.3) | | 0 (0) | |
| | FOLFIRI + Bevacizumab | 1 (8.3) | | 0 (0) | |
| | Irinotecan + 5-fluorouracil + Bevacizumab | 1 (8.3) | | 0 (0) | |
| | Docetaxel + Zoledronic acid | 1 (8.3) | | 0 (0) | |
| | Trastuzumab | 1 (8.3) | | 0 (0) | |
| | Not specified | 1 (8.3) | | 2 (18.2) | |

**G1:** PHMB group. **G2:** CLX group. **SD:** Standard Deviation.

**Table 2.** Level of oral mucositis and ratio between the two studied groups (G1 and G2) at three different times.

| OM level (WHO) | $t_0$ G1 N (%) | $t_0$ G2 N (%) | $t_1$ G1 N (%) | $t_1$ G2 N (%) | $t_2$ G1 N (%) | $t_2$ G2 N (%) |
|---|---|---|---|---|---|---|
| 0 | 11 (91.7) | 10 (90.9) | 7 (58.3) | 5 (50) | 11 (91.7) | 6 (60) |
| 1 | 0 (0) | 0 (0) | 2 (16.7) | 3 (30) | 1 (8.3) | 2 (20) |
| 2 | 1 (8.3) | 1 (9.1) | 1 (8.3) | 2 (20) | 0 (0) | 2 (20) |
| 3 | 0 (0) | 0 (0) | 1 (8.3) | 0 (0) | 0 (0) | 0 (0) |
| *p*-value | 0.976 | | 0.705 | | 0.203 | |

**G1:** PHMB group. **G2:** CLX group. **$t_0$:** Before antineoplastic treatment. **$t_1$:** During antineoplastic treatment. **$t_2$:** After antineoplastic treatment. **OM:** Oral mucositis. **WHO:** World Health Organization. ***p*-value:** At 5% significance level.

**Table 3.** Action of the mouthwashes (PHMB and CLX) in the mouth comparisons between two studied groups (G1 and G2).

| | $t_0$ G1 (%) | $t_0$ G2 (%) | $t_0$ *p*-value | $t_1$ G1 (%) | $t_1$ G2 (%) | $t_1$ *p*-value | $t_2$ G1 (%) | $t_2$ G2 (%) | $t_2$ *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| Was the rinsing possible and tolerable? | Yes (100) No (0) | Yes (100) No (0) | *** | Yes (100) No (0) | Yes (100) No (0) | *** | Yes (91.7) No (8.3) | Yes (100) No (0) | 0.522 |
| Did the rinsing become impossible at some moment? | Yes (0) No (100) | Yes (0) No (100) | *** | Yes (8.3) No (91.7) | Yes (0) No (100) | 0.522 | Yes (8.3) No (91.7) | Yes (0) No (100) | 0.522 |
| Did the solution used in the rinsing present a bitter or sweet flavor? | Bitter (58.3) Sweet (41.7) | Bitter (9.1) Sweet (90.9) | 0.019* | Bitter (58.3) Sweet (41.7) | Bitter (27.3) Sweet (72.7) | 0.140 | Bitter (41.7) Sweet (58.3) | Bitter (18.2) Sweet (81.8) | 0.222 |
| Was there a burning while rinsing with the solution? | Yes (8.3) No (91.7) | Yes (0) No (100) | 0.522 | Yes (16.7) No (83.3) | Yes (0) No (100) | 0.261 | Yes (8.3) No (91.7) | Yes (0) No (100) | 0.522 |
| Was there dry mouth after rinsing with the solution? | Yes (0) No (100) | Yes (0) No (100) | *** | Yes (0) No (100) | Yes (0) No (100) | *** | Yes (0) No (100) | Yes (0) No (100) | *** |
| Was there some discomfort after rinsing with the solution? | Yes (8.3) No (91.7) | Yes (0) No (100) | 0.522 | Yes (8.3) No (91.7) | Yes (0) No (100) | 0.522 | Yes (16.7) No (83.3) | Yes (0) No (100) | 0.261 |

**G1:** PHMB group. **G2:** CLX group. **$t_0$:** Before antineoplastic treatment. **$t_1$:** During antineoplastic treatment. **$t_2$:** After antineoplastic treatment. **OM:** Oral mucositis. **WHO:** World Health Organization. ***p*-value:** At 5% significance level. *: Statistically significant. ***:No statistics.

**Table 4.** Impact of the Oral Health in the Quality of Life – Comparison between two studied groups (G1 and G2).

| | $t_0$ G1 (%) | $t_0$ G2 (%) | $t_0$ *p*-value | $t_1$ G1 (%) | $t_1$ G2 (%) | $t_1$ *p*-value | $t_2$ G1 (%) | $t_2$ G2 (%) | $t_2$ *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| Functional limitation | 0.54 | 1.40 | 0.118 | ..31 | 1.48 | 0.608 | 0.62 | 1.23 | 0.288 |
| Physical pain | 0.42 | 1.60 | 0.019* | 0.81 | 1.61 | 0.347 | 0.78 | 1.39 | 0.487 |
| Psychological discomfort | 0.77 | 1.23 | 0.211 | 0.82 | 1.59 | 0.288 | 0.81 | 0.83 | 0.928 |
| Physical disability | 0.25 | 1.14 | 0.316 | 0.51 | 1.28 | 0.169 | 0.76 | 0.79 | 0.928 |
| Psychological disability | 0.417 | 0.8 | 0.288 | 0.133 | 0.473 | 0.566 | 0.067 | 0.545 | 0.880 |
| Social disability | 0..72 | 0.62 | 0.928 | 0.06 | 0.99 | 0.037* | 0.23 | 0.83 | 0.449 |
| Handicap | 0.13 | 0.87 | 0.134 | 0.34 | 1.47 | 0.169 | 0.38 | 1.20 | 0.379 |
| **Total** | **3.249** | **7.847** | **0.051** | **3.983** | **9.220** | **0.449** | **3.659** | **6.807** | **0.880** |

**G1:** PHMB group. **G2:** CLX group. **$t_0$:** Before antineoplastic treatment. **$t_1$:** During antineoplastic treatment. **$t_2$:** After antineoplastic treatment. **OM:** Oral mucositis. **WHO:** World Health Organization. ***p*-value:** At 5% significance level.

there was a significant difference ($p$=0.019) between groups in $t_0$, where seven (58.3%) G1 individuals found PHMB bitter and only one (9.1%) G2 subject found the substance CLX bitter. The questions concerning the action of the substance in the mouth. (Table 4)

The Oral Hygiene Index (OHI) in G1 at $t_0$ ranged from 1 to 2, with seven (77.8%) individuals presenting grade 1 and five (22.2%) presenting grade 2. In $t_1$ and $t_2$, the OHI ranged from 0 to 2, and at $t_1$ three patients (33.3%) were grade 0, five (55.6%) were grade 1 and one (11.1%) was grade 2. At $t_2$, four patients (40%) presented grade 0, four (40%) grade 1 and two (20%) grade 2.

In G2, the OHI ranged from 0 to 2 in all three times, with grade 0 being in two (20%) t0 and decreased to one (11.1%) at $t_1$ and $t_2$. OHI grade 1 was present in four (40%) patients at t0, three (33.3%) at $t_1$, and four (44.4%) at $t_2$. Grade OHI 2 was found in four (40%) at t0, five (55.6%) at $t_1$, and four (44.4%) at $t_2$.

Regarding OHIP-14, all dimensions had a weak impact at the three times. As to G2, all significative dimensions had a weak impact. Upon comparing both groups, there was a statistically significant difference in relation to the physical pain ($p$=0.019) at t0 and social inability ($p$=0.037) at $t_1$, both the highest in the G2.

## DISCUSSION.

Despite the wide use of PHMB in medicine, particularly in the area of wounds, there is scarce research on its use as an antiseptic for oral bacterial microbiota.[5,21,22] Knowing PHMB presents bactericidal action and a consequently ability to avoid secondary infections, its acceptance in a population already at risk for the development of oral mucositis and that present difficulty in the tolerance of oral mouth rinses is important.

However, the focus was not to evaluate the relationship between the substances and oral mucositis, but the perception and acceptance by these individuals regarding their use.

When referring to the amount of time the patient was able to keep the mouthwash in the mouth, 100% of the individuals in the PHMB group were able to maintain it for the full 60 seconds stipulated by the researchers. While in the group that used chlorhexidine, 18% of patients were unable to perform the mouth rinse for 60 seconds at t0 (Mean: 57.27 seconds and $p$=0.012), suggesting that chlorhexidine was less tolerable at first, different from what has been previously reported.[5] However, it was tolerable after a few days, as at $t_1$ and $t_2$ all the patients rinsed for the stipulated time.

Regarding the taste of the substances, most of the patients in the PHMB group reported that the substance was bitter at $t_0$, whereas in the group that used CLX, they reported that the substance was sweet. This difference was significant when comparing the two groups ($p$=0.019), indicating that chlorhexidine is a more pleasant substance.[22]

At both $t_1$ and $t_2$, there was a change in the flavor of the substances, a fact that can be attributed to dysgeusia, frequent palate changes in individuals under chemotherapy and/or radiotherapy.[23,24]

Regarding the Oral Hygiene Index, there was no difference between the groups or between the evaluations, this suggests that there is no difference in using PHMB 0.2% or chlorhexidine 0.12% for microbial biofilm control in these individuals. These results differ from previously published results, one that used a lower concentration than the one used in this study (0.04%)[25] and in another that used the same concentration.[21]

When assessing the impact of oral health on quality of life, using the OHIP-1419 questionnaire and comparing the groups, there exist a difference in the physical pain dimension at t0 ($p$=0.019) compared with the other times. In the PHMB group, this impact was weak, and it was medium in the group using chlorhexidine, this compromised the oral condition which in turn leads to a worse quality of life.

Another significant aspect was social impairment at $t_1$ ($p$=0.037), with both groups having a weak impact. However, the value of the group using chlorhexidine was over 16 times higher than the PHMB group (0.99 and 0.06, respectively). This suggests that PHMB impacts less on the social disability aspect than chlorhexidine.

One of the limitations of this study is the relationship between substance use, oral mucositis, and the impact of oral health on quality of life. Individuals who used PHMB had less oral mucositis after anti-neoplastic treatment, which may be related to a lower impact of oral health on the quality of life of these individuals.

This data should be observed with caution due to the heterogeneity of the individuals in this study, the number of participants and the fact that oral mucositis occurs independently of the action of topical

substances but it can be associated with the toxicity of chemotherapy and/or radiotherapy.[3]

In conclusion, these results suggest that PHMB has greater acceptance than CLX, and it could be a good alternative option for mouth rinsing with fewer adverse effects.

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**Ethics approval:** This study was approved by the Research Ethics Committee of the institution where it was carried out (CAEE 48742115.1.0000.5417).

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